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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MERTZ, PREMA MARIA	
ART UNIT	PAPER NUMBER
1646	

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12/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,291	KELLY, RODNEY WILLIAM	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-14,16,20-23,25-45,47-49,51,66,67,69,73-75,78 and 79* is/are pending in the application.

4a) Of the above claim(s) *3,4,20,21,27,45,47-49,51,66,67,69,73-75,78 and 79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5, 6-10, 12, 13-14, 16, 22-23, 25-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 11, 15, 17-19, 46, 50, 52-65, 68, 70-72, 76-77, 80-81 have been canceled previously and claim 24 has been canceled in the amendment filed 11/17/08. Amended claims 1, 7, 9, 22-23, 25-26 and previous claims 2, 5, 6, 8, 10, 12, 13, 14, 16, and 26 are under consideration by the Examiner

Pending claims 3-4, 20-21, 27-45, 47-49, 51, 66-67, 69, 73-75, 78-79, have been previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

2. Receipt of applicant's arguments and amendments filed on 11/17/2008 is acknowledged.

3. The following previous rejections and objections are withdrawn in light of applicants amendments filed on 11/17/2008:

(i) the objection to the specification for failure to comply with the sequence rules ; and

(ii) the provisional rejection of claims 1-2, 5-10, 12-14, 16, 22-26 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 28-40 of copending Application No. 10/576,437.

4. Applicant's arguments filed on 11/17/08 have been fully considered and were persuasive in part. The issues remaining and new issues are stated below.

Claim rejections-35 USC § 112, first paragraph, scope of enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 1-2, 5-10, 12-14, 16, 22-23, 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing tolerance in monocytes by increasing levels of granulysin, CD14, COX-2 and IL-10 and decreasing levels of CIITA and MHCII, the method comprising contacting monocyte cells with an effective amount of PGE2 and GM-CSF, does not reasonably provide enablement for a method of inducing tolerance to an antigen in a patient, the method comprising administering to the patient an agent which raises the effective cAMP concentration in a monocyte cell and granulocyte-macrophage colony stimulating factor (GMCSF) or a derivative thereof that has at least 50% of the ability of full length GMCSF to stimulate the production of granulocytes and macrophages from their progenitor cells and which in the presence of prostaglandin E causes monocytes to express IL-10, whereby said administering induces tolerance to an antigen in the patient and thereby treats or prevents an aberrant or undesired immune or inflammatory response to the antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth at pages 4-10 of the previous Office action of 5/16/2008.

Applicant argues that (i) the PTO alleges that the specification is enabling for a method of inducing tolerance to an antigen by administering PGE and GMCSF, but not for any other agent that raises the effective cAMP concentration in a monocyte cell together with GMCSF; and (ii) the PTO has based this conclusion on the allegation that the present application only provides

experimental support in relation to the combination of PGE and GMCSF. Applicant argues that that the PTO is incorrect, because both forskolin and probenicid were shown to have similar biological effects, at least in relation to IL-10, when used in combination with GMCSF (see Figures 6 and 9) and what these three agents have in common is their ability to raise cAMP levels in a monocyte cell *(see* Figure 5). Applicant argues that the description of results using these three agents (that achieve the recited effect) fully enables the recited language. However, contrary to Applicant's arguments, the claims as amended recite that the agent, GMCSF and prostaglandin E are administered to the patient. Therefore, in the absence of the recitation of the agent in the claim, the instant claims are not enabled because as amended the claims encompass agents that are not envisioned or described in the specification and the specification provides insufficient guidance to allow one to identify these other agents other than PGE2, forskolin and probenicid. There is no guidance provided in the instant specification as to how one of ordinary skill in the art would use the instant method with other agents other than those exemplified in the specification.

Applicant argues that the PTO alleges that the claims are enabled only for inducing tolerance to the antigen HLA-A2 for combating transplant rejection, and therefore it would require undue experimentation to determine which other antigens could be administered. Applicant respectfully disagrees and argues that pages 26-30 of the application list a large number of antigens that can be used with respect to specific conditions to be treated or prevented and that given the recitation of specific antigen useful for inducing tolerance for specific conditions, persons of skill in the art would be able to practice the invention without undue experimentation. However, contrary to Applicant's arguments, the claims as amended recite

"treats or prevents an aberrant or undesired immune or inflammatory response". "Preventing" implies determining in advance which patients will get the disease. The instant specification has failed to enable "preventing" autoimmune conditions such as primary myxoedema, thyrotoxicosis, pernicious anaemia, autoimmune atrophic gastris, Addison's disease, insulin-dependent diabetes mellitus (IDDM), Goodpasture's syndrome, myasthenia gravis, sympathetic ophthalmia, MS, autoimmune haemolytic anaemia, idiopathic leucopenia, ulcerative colitis, dermatomyositis, scleroderma, mixed connective tissue disease, rheumatoid arthritis, irritable bowel syndrome, SLE, Hashimoto's disease, thyroiditis, Behcet's disease, coeliac disease/dermatitis herpetiformis, and demyelinating disease, which are recited on page 27, lines 15-30, of the instant specification. Furthermore, the antigens involved in all these diseases are yet to be determined. Therefore, there is no guidance provided in the instant specification as to how one of ordinary skill in the art would use the instant method with other antigens other than antigen HLA-A2 exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Given the breadth of claims 1-2, 5-10, 12-14, 16, 22-23, 25-26, in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Claim rejections-35 USC § 112, first paragraph, written description

5b. Claims 1-2, 5-10, 12-14, 16, 22-23, 25-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record set forth at pages 10-12 of the previous Office action of 5/16/2008.

Applicant argues that the PTO has failed to consider the state of the art at the time the present invention was made, a number of GM-CSF variants/derivatives were known in the art, including those described in the application at pages 12-14 as well as those described in PCT Publ. WO 1989/010403, GM-CSF from various mammals were also known (see, e.g., Genbank Associates CAA26821, mouse; NP 776452, bovine; BAA04649, pig; AAG 16626, rhesus monkey) and thus, persons of skill in the art would have understood that GM-CSF is not limited to the human GM-CSF of SEQ ID NO:2. However, contrary to Applicants arguments, except for human GM-CSF consisting of the amino acid sequence set forth in SEQ ID NO:2, Applicant has failed to provide a written description for any other GM-CSF composition.

The instant specification does not provide an adequate description for "granulocyte macrophage colony stimulating factor (GMCSF) or a derivative thereof that has at least 50% of the ability of full length GMCSF to stimulate the production of granulocytes and macrophages from their progenitor cells as encompassed by the scope of claims 1-2, 5-10, 12-14, 16, 22-23, 25-26. In the decision of *The Regents of the University of Calfornia v. Eli Lilly and Company*, 43 USPQ2d 1398 (CAFC 1997), the court held that:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997), *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" (T)he description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In the instant application, there is a complete lack of written description for a GM-CSF derivative encompassed by the scope of the claims, other than for human GM-CSF of SEQ ID NO:2. Applicant asserts that persons of skill in the art fully appreciated the various GM-CSF and derivatives that were known in the art, whereas the cited caselaw involved claims to novel products or use of novel products where only a single species (or in some cases, no species) were

disclosed and that is clearly very different from the circumstances here, where a relatively large number of species were previously known in the art. However, Applicant's assertion is false and judicially unsound. To the contrary the following decisions*: University of Rochester v. G.D. Searle & Co.,* 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co.,* CAFC (03-1304) decided February 13, 2004 and *Noelle v. Lederman*, decided January 20, 2004 are also applicable in the instant case.

In *University of Rochester v. G.D. Searle & Co.,* a patent directed to method for inhibiting prostaglandin synthesis in human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since the patent described the compound's desired function of reducing activity of enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since the invention consisted of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since the specification did not indicate that the compounds were available in a public depository, the claimed treatment method could not be practiced without the compound. The written description requirement must still be met in some way so as to "describe the claimed invention so that one skilled in the art can recognize what is claimed." *Enzo*, 323 F.3d at 968. The Court further explained that:

> [T]he appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. . . . A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described

> even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice. [Regents of the Univ. of Cal. v.] Eli Lilly [& Co., Inc.], 119 F.3d [1559,] 1568 [(Fed. Cir. 1997) ("Lilly")] . . . . The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. Id. *Enzo*, 323 F.3d at 968.

Thus, the Court in *University of Rochester* held that the inventors could not be said to have "possessed" the claimed invention without knowing of a compound or method certain to produce the compound. Thus, the patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compounds defined only by their desired properties.

Therefore, similar to *University of Rochester,* here, the full breadth of the claims fails to meet the written description provision of 35 U.S.C. §112, first paragraph.

In the *Noelle* case, the claims in the Noelle application, were directed to the genus, murine, chimeric, humanized and human forms of CD40CR monoclonal antibody. An interference was set up between the Noelle application and the Lederman patent 5,474,771, which claimed the human form of CD40CR monoclonal antibody. The Court concluded that the Board made a detailed analysis of this court's precedent pertaining to the doctrine of written description, focusing on the holding from Regents of the University of California v. Eli Lilly & Co. that an "adequate written description of a DNA sequence claim requires a precise definition, such as structure, formula, chemical name, or physical properties." 119 F.3d 1559, 1566 (Fed.

Cir. 1997). The Board analogized the DNA claims from Regents to the antibodies in Noelle's application. Accordingly, the Board held that Noelle's claims regarding the genus and human claims from the 08/742,480 application lacked written description support in the specification of Noelle's earlier 07/835,799 application because Noelle failed to describe any structural features of the human or genus antibodies or antigens. In other words, the Board found that the claims covering the genus and human antibodies constituted new matter because they lacked adequate written description in Noelle's earlier '799 application. The Board did not reject the claims, but rather denied them the benefit of the earlier filing date of Noelle '799.

The Court in Noelle held that the written description requirement has been defined many times by the court, but perhaps most clearly in Vas-Cath. The court held as follows:

> 35 U.S.C. § 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.

Vas-Cath, 935 F.2d at 1563-64 (emphasis in original). Thus, the test to determine if an application is to receive the benefit of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application. An earlier application that describes later-claimed genetic material only by a statement of function or result may be

insufficient to meet the written description requirement. See Regents, 119 F.3d at 1566. This court has held that a description of DNA "requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. (quoting Fiers v. Revel, 984 F.2d 1164, 1170 (Fed. Cir. 1993)). Therefore, this court has held that statements in the specification describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead "an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1566-67 (quoting Fiers, 984 F.2d at 1171).

Indeed, the court in Enzo Biochem v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002) ("Enzo Biochem II"), stated that "the written description requirement would be met for all of the claims [of the patent at issue] if the functional characteristic of [the claimed invention was] coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." Also, the court held that one might comply with the written description requirement by depositing the biological material with a public depository such as the American Type Culture Collection ("ATCC"). Id. at 970. The court proffered an example of an invention successfully described by its functional characteristics. The court stated:

> For example, the PTO would find compliance with 112, paragraph 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of

antibody binding, and the fact that the antibody technology is well developed and mature. Id.

The court adopted the USPTO Guidelines as persuasive authority for the proposition that a claim directed to "any antibody, which is capable of binding to antigen X" would have sufficient support in a written description that disclosed "fully characterized antigens." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/menu/written.pdf (last visited Jan. 16, 2003) (emphasis added).

Therefore, based on past precedent, the Court in *Noelle* concluded that as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.

Therefore, the CAFC decisions in *Noelle* and *University of Rochester* are controlling precedents for the claims in the instant case and it is suggested that Applicant visit these decisions. Contrary to Applicant's arguments, the Examiner is not improperly applying a heightened written description standard here. There is absolutely no written description for the claimed subject matter drawn to a method of administering "a derivative" of GM-CSF. Therefore, Applicants were not in possession of the mutant GM-CSF polypeptides to be used in the claimed method.

Claim rejections-35 U.S.C. 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-2, 5-10, 12-14, 16, 22-23, 25-26, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as vague and indefinite for several reasons.

Amended claim 1, line 7, is vague and indefinite because it recites "…which in the presence of prostaglandin E causes monocytes to express IL-10". It is unclear if "prostaglandin E" is the "agent" administered or if "prostaglandin E" is administered in addition to the agent.

Similarly, amended claim 25, lines 4-5, is vague and indefinite because it recites "…which in the presence of prostaglandin E causes monocytes to express IL-10". It is unclear if "prostaglandin E" is the "agent" administered or if "prostaglandin E" is administered in addition to the agent.

Claim 1, line 9, is vague and indefinite because it recites "aberrant or undesired immune or inflammatory response". The metes and bounds of these conditions is unclear.

Applicant argues that the rejection of claim 1 for failing to identify the condition that the patient is suffering from is overcome by the amendment, this invention is clearly applicable to various different patients, each of whom requires tolerance to different antigens and that the conditions are associated with either aberrant or undesired immune or inflammatory response to

the antigen. However, contrary to Applicants arguments, it is unclear which immune responses are aberrant or undesired because Applicants have failed to recite such conditions in the claim.

Applicant argues that the rejection of claims 1, 22 and 25 for use of the term "GMCSF or a derivative thereof" is overcome by the above amendment because the specification clearly recites that GMCSF or its variants or derivatives can be used to practice the invention, and defined these derivatives as a fragment, fusion or sequence variant of GMCSF that has at least 50% of the ability of full length GMCSF to stimulate the production of granulocytes and macrophages from their progenitor cells and which in the presence of prostaglandin E causes monocytes to express IL-10. However, contrary to Applicant's arguments, it is unclear which of the numerous derivatives of GM-CSF would have at least 50% of the ability of full length GMCSF to stimulate the production of granulocytes and macrophages from their progenitor cells and which in the presence of prostaglandin E causes monocytes to express IL-10. It is suggested that, to obviate this rejection, Applicant recite the derivatives of GM-CSF that are recited in the instant specification.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7a. Claims 1-2, 5-8, 9, 12-14, 16, 22, are rejected under 35 U.S.C. 103(a) as unpatentable over Piquet-Pellorce et al (1991) in view in of Owens et al (U.S. Patent No. 5,851,784).

This rejection is maintained for reasons of record set forth at pages 14-16 of the previous Office action of 5/16/2008.

Applicant argues that Piquet-Pellorce teaches that the administration of PGE2 and GMCSF to isolated bone marrow cells increases intracellular cAMP levels, the PTO has acknowledged that Piquet-Pellorce is silent regarding inducing tolerance to an antigen and that Owens is cited for teaching that PDE IV selective inhibitors, such as rolipram, also increase intracellular cAMP levels. Applicant argues that the PTO has failed to set forth a *prima facie* basis for this rejection because the combination of references fails to teach or suggest each and every limitation of the claimed invention, in particular, the combination of references fails to teach or suggest the administering of PGE2 and GMCSF to a patient, let alone where such administering is effective induce tolerance to an antigen in the patient and thereby treat or

prevent an aberrant or undesired immune or inflammatory response to the antigen. Applicant argues that because neither of these limitations is taught or suggested, the rejection of claims 1, 2, 5-9, 12-14, 16 and 22 for obviousness over Piquet-Pellorce in view of Owens is improper and should be withdrawn. However, contrary to Applicants arguments, there is no step in instant claim 1 that recites that an antigen is administered in the claimed method.

Piquet-Pellorce et al teaches a method of administering PGE2 and GMCSF to bone marrow cells to potentiate histamine release and that both PGE2 and GMCSF together increase intracellular cAMP content in a synergistic manner (see abstract; page 2378, last paragraph; page 2379, Figures 1-3; page 2380, first 15 lines). However, the reference does not disclose further administering a phosphodiesterase (PDE) inhibitor in the claimed method.

Owens et al ('784) teaches that intracellular cAMP levels are regulated by degradation by PDE (column 1, lines 9-15) and that PDE IV activity is markedly inhibited by PDE IV selective inhibitors such as rolipram and denbufylline (see column 12, lines 64-67).

Therefore, at the time the invention was made, it would have been prima facie obvious to a person of ordinary skill in the art to administer PGE2 and GMCSF as taught by Piquet-Pellorce et al together with a PDE IV inhibitor as taught by Owens et al. The motivation for doing so would have been because Owens teaches that inhibition of PDE activity markedly increases cAMP levels. Therefore, the combination of references renders obvious claims 1-2, 5-8, 9, 12-14, 16, 22.

In addition, the Court in *KSR* held that "Neither §103's enactment nor *Graham's* analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent

based on the combination of elements found in the prior art." *KSR v. Teleflex*, 550 U.S., 82 USPQ2d 1385, 1389 (2007). The *KSR* court stated that "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR* at 1389.

Furthermore, the KSR court concluded that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in *KSR:*

When there is motivation
"to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product is not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.,* 127 S. CI. 1727, 82 USPQ2d 1385, 1397 (2007).

In the instant case the claims would have been obvious in view of the prior art references because one of ordinary skill in the art would have been motivated to administer PGE2, GMCSF and a PDE IV inhibitor because each of the references teach the known functions and advantages of administering such to increase cAMP levels.

Conclusion

No claim is allowed.

Claims 1-2, 5-10, 12-14, 16, 22-23, 25-26, are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

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